IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Ching-Fen HSIAO et al.

Serial No: 10/784,499 Group Art Unit: 1615

Filing Date: 02/23/2004 Examiner: Tran, Susan T

For: Sustained Release Tamsulosin Formulation

DECLARATION UNDER 37 C.F.R. §1.132

We, Ching-fen Hsiao, Yi-Loong Wang, Ya-sheng Yang and Ya-ching Chang Chien, declare that:

1. We are all inventors of the invention claimed in the subject application and are fully familiar with the subject matter thereof as well as the references relied upon by the Examiner in the prosecution of this application;

2. We supervised the following experiments that further demonstrate that the physical characteristics of sustained release Tamsulosin formulation produced in accordance with the present invention differ from the citation (Vaghefi's application) by providing experiment and data.

3. Sustained release Tamsulosin formulation that was produced according to Example 5 in this application was employed in the following experiment to show the physical differences between the present application and Vaghefi's application, and the experimental data are shown below.

Physical differences between the present invention and the citation (Vaghefi)

The present application relates to a sustained release Tamsulosin formulation having Tamsulosin or a pharmaceutical acceptable salt, a hydrophobic polymer, a microsphere forming agent and a diluent. The procedure of the present application was that the foregoing components were mixed well with a knead solution at 1 atm to obtain a mixture. The mixture was put into an extruding granulator having a hole with a diameter of 0.5 to 2.0 mm to extrude the mixture and obtained a column 0.5 to 2.0 mm in length. Then each column was cut and formed into microspheres. Consequently, all components including the active ingredient of the formulation of the present application were mixed uniformly. The microsphere obtained from Example 5 in the present application was compared with the citation (Vaghefi), and scanning electron micrograph pictures were taken. Two scanning electron micrograph pictures are attached.

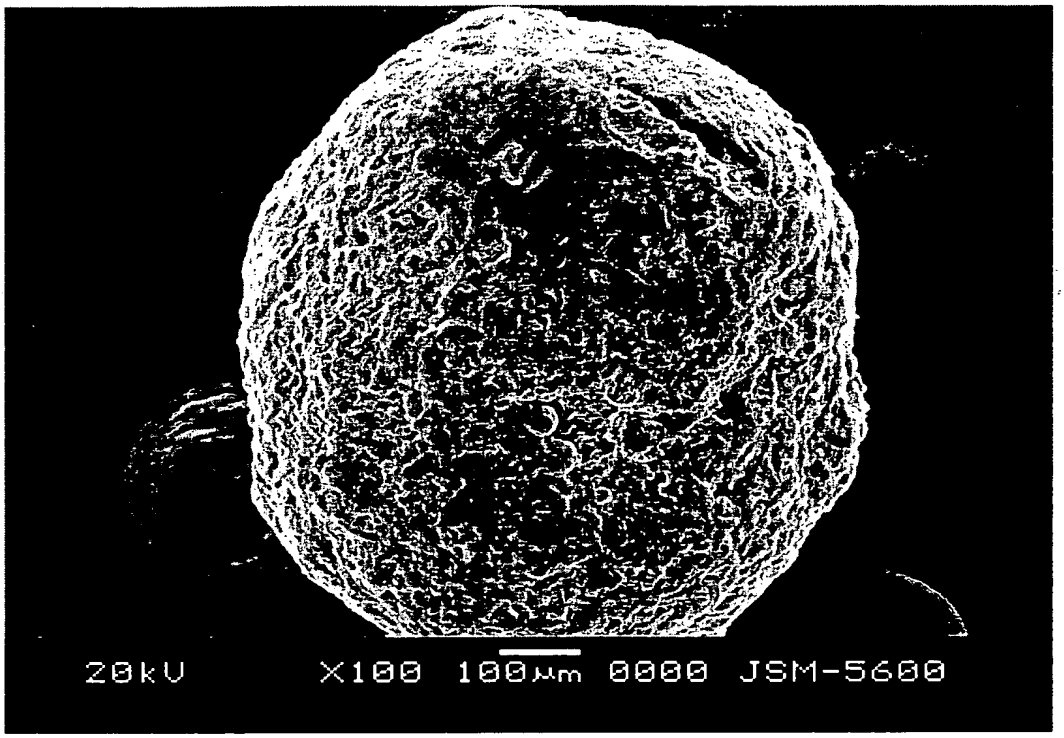

Fig. 1

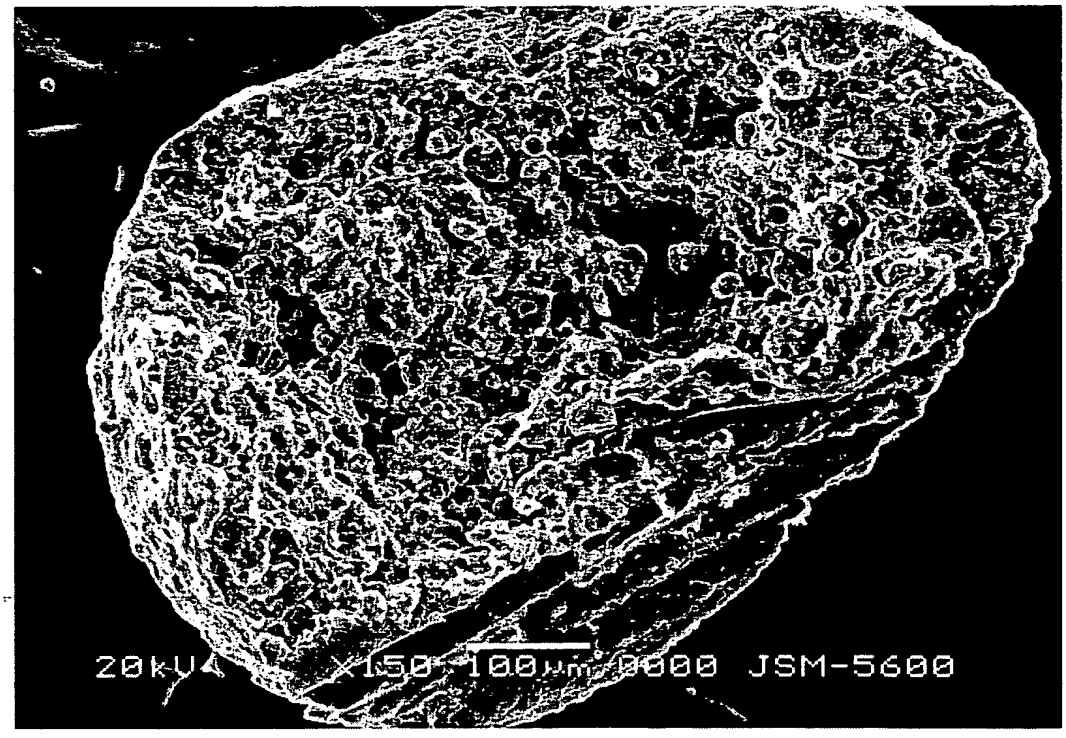

Fig. 2

Fig. 1 is a scanning electron micrograph picture of the surface of a

microsphere obtained from the present application. A scale marker of 100 microns is in the bottom of the picture. Fig. 2 is a scanning electron micrograph picture of a cross-section of a microsphere obtained from the present application. A scale marker of 100 microns is in the bottom of the picture.

First, the components of the microsphere of the present application are well mixed and are continuously distributed. With reference to Fig. 1, the microsphere of the present application has a rough surface. The rough surface of the microsphere indicates that all components including the active ingredient and excipients of the microsphere are uniformly mixed.

Second, with reference to Fig. 2, the view of the interior region of the microsphere of the present application also shows a continuous distribution, and the microsphere doesn't show an identifiable interior region.

Third, the procedure described in the present application is simple.

According to the experimental data, that the sustained release Tamsulosin formulation of the present application has smooth outer surface and the components in the microsphere are uniformly mixed and present continuos distribution is clear.

4. We have read the Vaghefi *et al.* (US 2003/0157326 A1) application cited by the Examiner and have the following comments.

The microsphere obtained from Vaghefi *et al.* application has an interior region and a surface region. As described in US 2003/0157326 A1 Vaghefi *et al.,* the microsphere comprises an interior region comprising a plurality of microcapsules consisting of a core of bioactive compound coated with material containing a charged organic group and a surface region

substantially free of said bioactive compound.

With reference to Fig. 1 of the citation (Vaghefi), the surface of the microsphere of the citation (Vaghfi) is smooth. With further reference to Fig. 10 of the citation (Vaghefi), the active ingredient is contained inside the microsphere.

With reference to Figs. 2 to 5 and 10 of the citation (Vaghefi), the microsphere of the citation (Vaghefi) has a definite interior region that contains a bioactive compound and excipients.

Also, the procedure described in the citation (Vaghefi) is complex. The procedure of the citation (Vaghefi) comprises spraying a flowable dispersion of bioactive micron-sized organic particles containing charged organic moieties in a water insoluble fluid matrix into a chilling zone, under conditions that form droplets of said dispersion, and maintaining the fluidity of said droplets for a time sufficient to distribute homogenously said particles in said droplets, and allowing said droplets to solidify into said microspheres.

5. Comparison Table:

		Vaghefi	The present application
Physical Characteristic	Interior region	Identifiable interior region	No identifiable interior region
	Surface region	Smooth surface region	Rough surface region
Components		Bioactive compounds and	Bioactive compounds and

	expients are stored inside the interior region	expients are well mixed and present continuos distribution in the interior region
Procedure	Complex	Simple

Compared to the procedure described in the citation (Vaghefi), the procedure to formulate sustained release Tamsulosin described in the present application is simply mixing all components well. The procedure described in the present application is simpler than the procedure in the citation (Vaghefi). Different manufacturing procedures to prepare the microspheres will obtain different physical characteristic products.

To conclude, the physical characteristics of microspheres in the present application and the citation (Vaghefi) are very different, and an ordinarily skilled person in the art cannot anticipate the present application.

6. We understand fully the content of this declaration.

7. We, Ching-fen Hsiao, Yi-Loong Wang, Ya-sheng Yang and Ya-ching Chang Chien, the undersigned declarants, declare further that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statement, under Section 1001, of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the

application or any patent issuing thereon. Therefore, we make this declaration to request an impartial consideration of our invention for a patent.

Signed this 18 day of February, 2005.

Ching-fen Hsiao

Ching-fen Hsiao

Signed this 18 day of Feb., 2005.

Yi-Loong Wang

Yi-Loong Wang

Signed this 18 day of Feb., 2005.

Ya-sheng Yang

Ya-sheng Yang

Signed this 19 day of Feb., 2005.

Ya-ching Chang Chien

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We, Ching-fen Hsiao, Yi-Loong Wang, Ya-sheng Yang and Ya-ching Chang Chien, declare that:

1. We are inventors in the subject application and are fully familiar with the subject matter of the subject application as well as the references relied upon by the Examiner in the prosecution of this application;

2. We supervised the following experiments that further demonstrate the material characteristics of sustained release Tamsulosin formulation produced in accordance with the present invention differ from the citation (Fukui's application) by providing experiments and data.

3. Sustained release Tamsulosin formulation that was produced according to Example 5 in this application was employed in the following experiments to show the material difference between the present application and Fukui's application, and the experimental data are shown below.

4. Material differences between the present invention and the citation

(Fukui)

The material difference between the products of the present application and the citation (Fukui) is the concentration of the aqueous release controlling agent employed. A high concentration of cellulose derivatives, as a kind of aqueous release controlling agent, in the citation will increase friction among the granulates in a mixture during granulation and cause an elevated temperature. The elevated temperature will cause acrylic acid polymers to become glue-like during granulation. The glue-like condition causes technical difficulties with the granulation.

The concentration of aqueous controlling agent in the present application is 10% to 65%. The lower concentration of aqueous release controlling agent prevents the mixture from acquiring a glue-like characteristic during an elevated temperature. The following table shows the results of a lower concentration of aqueous release controlling agent used in the present application under different temperatures.

Temperature	30℃	40℃	50℃	60℃	80℃
Mixture before kneading	well mixed mixture	well mixed mixture	well mixed mixture	well mixed mixture	well mixed mixture
Mixture after kneading	well mixed mixture	well mixed mixture	well mixed mixture	well mixed mixture	well mixed mixture

5. We have read the Fukui *et al.* (US 4,772,475) patent cited by the Examiner and have the following comments.

The concentration of the aqueous controlling release agent used in Fukui *et al.* patent is in the range 50% to 150%. An excerpt from the "*Handbook of Pharmaceutical Excipients*" (fourth edition) for submission to the USPTO proves the glue-like condition is caused by acrylic acid polymers at an elevated temperature. The excerpt is attached.

6. To conclude, the present application teaches a lower concentration

of aqueous release controlling agent to overcome the glue-like problem caused by acrylic acid polymers at high temperature.

According to the present application, practitioners would not encounter the foregoing technical difficulties since the concentration of the cellulose derivatives employed is not as high as that in the citation (Fukui).

7. We understand fully the content of this declaration.

8. We, Ching-fen Hsiao, Yi-Loong Wang, Ya-sheng Yang and Ya-ching Chang Chien, the undersigned declarants, declare further that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statement, under Section 1001, of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon. Therefore, we make this declaration to request an impartial consideration of our invention for a patent.

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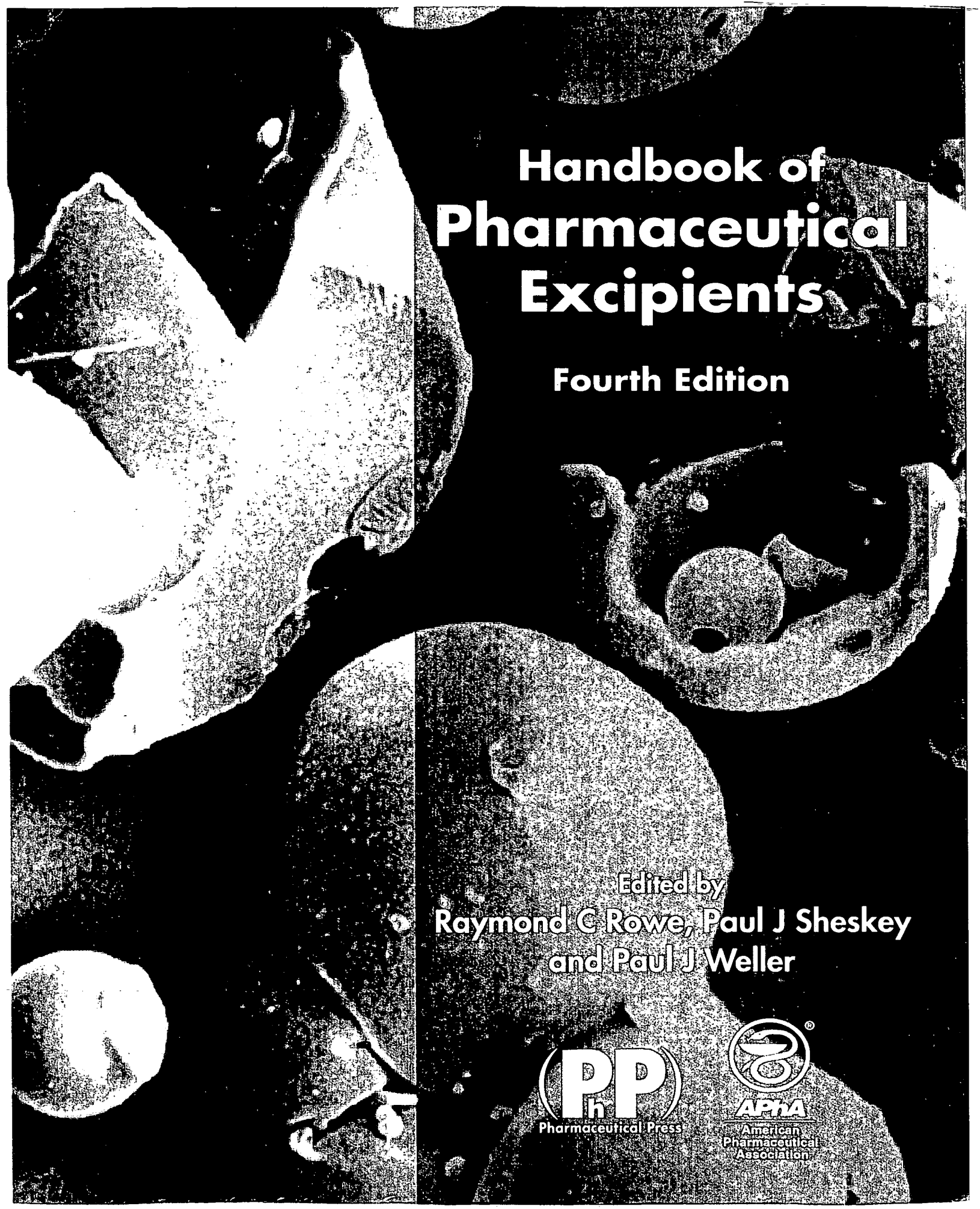


Handbook of Pharmaceutical Excipients

Fourth Edition

Edited by
Raymond C Rowe, Paul J Sheskey
and Paul J Weller

Pharmaceutical Press
APhA American Pharmaceutical Association

Carbomer

1 Nonproprietary Names

BP: Carbomers
PhEur: Carbomera
USPNF: Carbomer
Note that the USPNF 20 contains several individual carbomer monographs; *see* Sections 4 and 9.

2 Synonyms

Acritamer; acrylic acid polymer; *Carbopol*; carboxy polymethylene, polyacrylic acid; carboxyvinyl polymer; *Pemulen*; *Ultrez*.

3 Chemical Name and CAS Registry Number

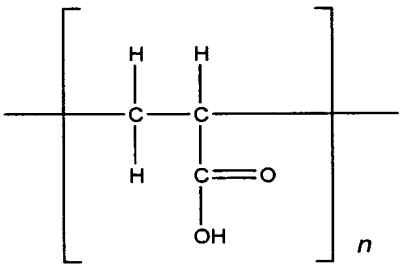
Carbomer [9003-01-4]

Note that carbomer 910, 934, 934P, 940, 941, 971P, and 974P resins share the common CAS registry number 9003-01-4. Carbomer 1342 is a copolymer and has a different CAS registry number.

4 Empirical Formula Molecular Weight

Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allylsucrose or allyl ethers of pentaerythritol. They contain between 56% and 68% of carboxylic acid (COOH) groups calculated on the dry basis. The BP 2001 and PhEur 2002 have a single monograph describing carbomer; the USPNF 20 contains several monographs describing individual carbomer grades that vary in aqueous viscosity and in labeling for oral or non-oral use. The molecular weight of carbomer resins is theoretically estimated at 7×10^5 to 4×10^9. In an effort to measure the molecular weight between crosslinks, M_C, researchers have extended the network theory of elasticity to swollen gels and have utilized the inverse relationship between the elastic modulus and M_C.[1–3] Estimated M_C values of 237 600 g/mol for *Carbopol 941* and of 104 400 g/mol for *Carbopol 940* have been reported.[4] In general, carbomer resins with lower viscosity and lower rigidity will have higher M_C values. Conversely, higher-viscosity, more rigid carbomer resins will have lower M_C values.

5 Structural Formula



Acrylic acid monomer unit in carbomer resins.

Carbomer polymers are formed from repeating units of acrylic acid. The monomer unit is shown above. The polymer chains are crosslinked with allyl sucrose or allylpentaerythritol. *See also* Section 4.

6 Functional Category

Bioadhesive; emulsifying agent; release-modifying agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Carbomers are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. Formulations include creams, gels, and ointments for use in ophthalmic,[5–7] rectal,[8,9] and topical preparations.[10–12] Carbomer grades, even with a low residual benzene content, such as carbomer 934P, are no longer included in the PhEur 2002. However, carbomer having low residuals only of other solvents than the ICH-defined 'Class I OVI solvents' may be used in Europe. Carbomer having low residuals only of ethyl acetate, such as carbomer 971P or 974P, may be used in oral preparations, in suspensions, tablets, or sustained release tablet formulations.[13–17] In tablet formulations, carbomers are used as dry or wet binders and as a rate controlling excipient. In wet granulation processes, water or an alcohol–water blend is used as the granulating fluid. Anhydrous organic solvents have also been used, with the inclusion of a polymeric binder. The tackiness of the wet mass can be reduced with the addition of certain cationic species to the granulating fluid[18] or, in the case of water, with talc in the formulation. Carbomer resins have also been investigated in the preparation of sustained-release matrix beads,[18] as enzyme inhibitors of intestinal proteases in peptide-containing dosage forms,[19,20] as a bioadhesive for a cervical patch[21] and for intranasally administered microspheres,[22] and in magnetic granules for site-specific drug delivery to the esophagus.[23] Carbomers are also employed as emulsifying agents in the preparation of oil-in-water emulsions for external use. For this purpose, the carbomer is neutralized partly with sodium hydroxide and partly with a long-chain amine such as stearylamine. Carbomer 951 has been investigated as a viscosity-increasing aid in the preparation of multiple emulsion microspheres.[24] Carbomers are also used in cosmetics. *See* Table I.

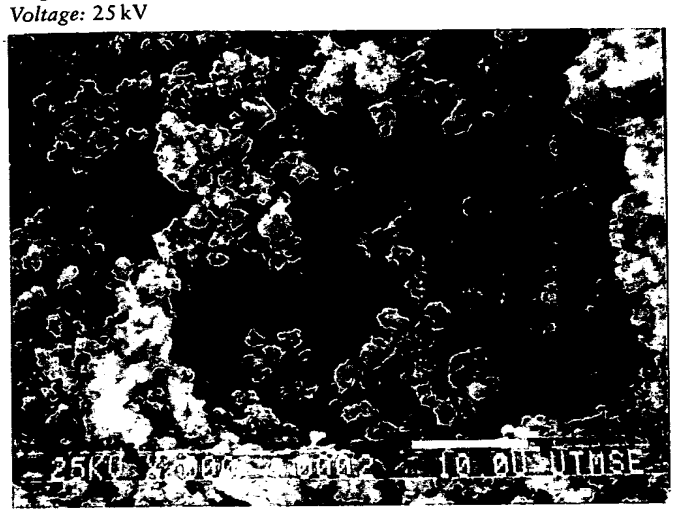
Table I: Uses of carbomers.

Use	Concentration (%)
Emulsifying agent	0.1–0.5
Gelling agent	0.5–2.0
Suspending agent	0.5–1.0
Tablet binder	5.0–10.0

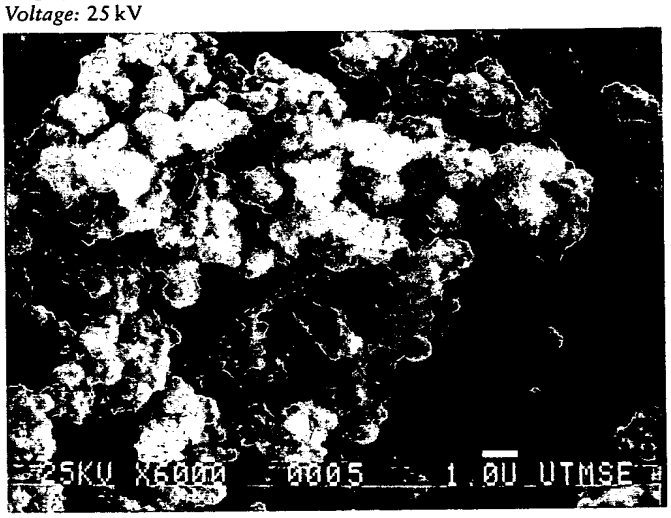
8 Description

Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a slight characteristic odor.

SEM: 1
Excipient: Carbomer 971P (*Carbopol 971P*)
Manufacturer: BF Goodrich
Magnification: 2000 ×
Voltage: 25 kV



SEM: 2
Excipient: Carbomer 971P (*Carbopol 971P*)
Manufacturer: BF Goodrich
Magnification: 6000 ×
Voltage: 25 kV



9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for carbomers.

Test	PhEur 2002 (Suppl 4.2)	USPNF 20
Identification	+	+
Characters	+	—
Aqueous viscosity (mPa s)	300–115 000	—
Carbomer 910 (1.0% w/v)	—	3 000–7 000
Carbomer 934 (0.5% w/v)	—	30 500–39 400
Carbomer 934P (0.5% w/v)	—	29 400–39 400
Carbomer 940 (0.5 w/v)	—	40 000–60 000
Carbomer 941 (0.5 w/v)	—	4 000–11 000
Carbomer 1342 (1.0% w/v)	—	9 500–26 500
Loss on drying	⩽3.0%	⩽2.0%
Sulfated ash	⩽4.0%	—
Heavy metals	⩽20 ppm	⩽0.002%
Benzene	⩽2 ppm	—
Carbomer 910	—	⩽0.5%
Carbomer 934	—	⩽0.5%
Carbomer 934P	—	⩽0.01%
Carbomer 940	—	⩽0.5%
Carbomer 941	—	⩽0.5%
Carbomer 1342	—	⩽0.2%
Free acrylic acid	⩽0.25%	—
Assay (COOH content)	56.0–68.0%	56.0–68.0%

Note that the USPNF 20 has several monographs for different carbomer grades, while the BP 2001 and the PhEur 2002 have only a single monograph. Other grades of carbomer meet the existing USPNF 20 standards as indicated above. Carbomer 974P is covered by the monograph for carbomer 934P in the USPNF 20. Likewise, carbomer 980 meets the specifications for carbomer 940; carbomers 971P and 981 meet the monograph limits for carbomer 941. Carbomer resins are also covered either individually or together in other pharmacopeias. Unless otherwise indicated, the test limits shown above apply to all grades of carbomer.

10 Typical Properties

Acidity/alkalinity:
pH = 2.7–3.5 for a 0.5% w/v aqueous dispersion
pH = 2.5–3.0 for a 1% w/v aqueous dispersion

Density (bulk): 1.76–2.08 g/cm^3

Density (tapped): 1.4 g/cm^3

Glass transition temperature: 100–105°C

Melting point: decomposition occurs within 30 minutes at 260°C. *See* Section 11.

Moisture content: normal water content is up to 2% w/w. However, carbomers are hygroscopic and a typical equilibrium moisture content at 25°C and 50% relative humidity is 8–10% w/w. The moisture content of a carbomer does not affect its thickening efficiency, but an increase in the moisture content makes the carbomer more difficult to handle because it is less readily dispersed.

Particle size distribution: primary particles average about 0.2 μm in diameter. The flocculated powder particles average 2–7 μm in diameter and cannot be broken down into the primary particles. Recently, a granular carbomer having a particle size in the range 180–425 μm has been introduced. Its bulk and tap densities are also higher than those of other carbomers.

Solubility: soluble in water and, after neutralization, in ethanol (95%) and glycerin.
Although they are described as 'soluble', carbomers do not dissolve but merely swell to a remarkable extent, since they are three-dimensionally crosslinked microgels. Furthermore, the pharmacopeial specifications are unclear, in that neutralization with long-chain aliphatic amines or ethoxylated long-chain amines is required for swellability in ethanol, and with water-soluble amines for swellability in glycerin.

Specific gravity: 1.41

Viscosity (dynamic): carbomers disperse in water to form acidic colloidal dispersions of low viscosity that, when

neutralized, produce highly viscous gels. Carbomer powders should first be dispersed into vigorously stirred water, taking care to avoid the formation of indispersible lumps, then neutralized by the addition of a base. BF Goodrich has introduced the *Carbopol ETD* and *Ultrez 10* series of carbomers to help overcome some of the problems of dispersing the powder into aqueous solvents. These carbomer resins wet quickly yet hydrate slowly, while possessing a lower unneutralized dispersion viscosity. Agents that may be used to neutralize carbomer polymers include amino acids, borax, potassium hydroxide, sodium bicarbonate, sodium hydroxide, and polar organic amines such as triethanolamine. Lauryl and stearyl amines may be used as gelling agents in nonpolar systems. One gram of carbomer is neutralized by approximately 0.4 g of sodium hydroxide. During preparation of the gel, the solution should be agitated slowly with a broad, paddlelike stirrer to avoid introducing air bubbles. Neutralized aqueous gels are more viscous at pH 6–11. The viscosity is considerably reduced at pH values less than 3 or greater than 12 or in the presence of strong electrolytes.[18,25] Gels rapidly lose viscosity on exposure to ultraviolet light, but this can be minimized by the addition of a suitable antioxidant. *See also* Section 11.

11 Stability and Storage Conditions

Carbomers are stable, hygroscopic materials that may be heated at temperatures below 104°C for up to 2 hours without affecting their thickening efficiency. However, exposure to excessive temperatures can result in discoloration and reduced stability. Complete decomposition occurs with heating for 30 minutes at 260°C. Dry powder forms of carbomer do not support the growth of molds and fungi. In contrast, microorganisms grow well in unpreserved aqueous dispersions and therefore an antimicrobial preservative such as 0.1% w/v chlorocresol, 0.18% w/v methylparaben–0.02% w/v propylparaben, or 0.1% w/v thimerosal should be added. The addition of certain antimicrobials, such as benzalkonium chloride or sodium benzoate, in high concentrations (0.1% w/v) can cause cloudiness and a reduction in viscosity of carbomer dispersions. Aqueous gels may be sterilized by autoclaving[7] with minimal changes in viscosity or pH, provided care is taken to exclude oxygen from the system, or by gamma irradiation, although this technique may increase the viscosity of the formulation.[26,27] At room temperature, carbomer dispersions maintain their viscosity during storage for prolonged periods. Similarly, dispersion viscosity is maintained, or only slightly reduced, at elevated storage temperatures if an antioxidant is included in the formulation or if the dispersion is stored protected from light. Exposure to light causes oxidation that is reflected in a decrease in dispersion viscosity. Stability to light may be improved by the addition of 0.05–0.1% w/v of a water-soluble UV absorber such as benzophenone-2 or benzophenone-4 in combination with 0.05–0.1% w/v edetic acid. The UV stability of carbomer gels may also be improved by using triethanolamine as the neutralizing base; *see* Section 10.

Carbomer powder should be stored in an airtight, corrosion-resistant container in a cool, dry place. The use of glass, plastic, or resin-lined containers is recommended for the storage of formulations containing carbomer. Packaging in aluminum tubes usually requires the formulation to have a pH less than 6.5, and packaging in other metallic tubes or containers necessitates a pH greater than 7.7 to prolong carbomer stability.

12 Incompatibilities

Carbomers are discolored by resorcinol and are incompatible with phenol, cationic polymers, strong acids, and high levels of electrolytes. Certain antimicrobial adjuvants should also be avoided or used at low levels, *see* Section 11. Trace levels of iron and other transition metals can catalytically degrade carbomer dispersions. Intense heat may be generated if a carbomer is in contact with a strong basic material such as ammonia, potassium or sodium hydroxide, or strongly basic amines.

Certain amino-functional actives form water-insoluble complexes with carbomer; often this can be prevented by adjusting the solubility parameter of the fluid phase using appropriate alcohols and polyols.

Carbomers also form pH-dependent complexes with certain polymeric excipients. Adjustment of solubility parameter can also work in this situation.

13 Method of Manufacture

Carbomers are synthetic, high-molecular-weight, crosslinked polymers of acrylic acid. These poly(acrylic acid) polymers are crosslinked with allylsucrose or allylpentaerythritol. The polymerization solvent used most commonly was benzene; however, some of the newer commercially available grades of carbomer are manufactured using either ethyl acetate or a cyclohexane–ethyl acetate cosolvent mixture. The *Carbopol ETD* resins are produced in the cosolvent mixture with a proprietary polymerization aid, and these resins are crosslinked with a polyalkenyl polyether.

14 Safety

Carbomers are used extensively in nonparenteral products, particularly topical liquid and semisolid preparations. They may also be used in oral formulations, although only certain grades can be used; *see* Section 18. Acute oral toxicity studies in animals indicate that carbomer 934P has a low oral toxicity, with doses up to 8 g/kg being administered to dogs without fatalities occurring. Carbomers are generally regarded as essentially nontoxic and nonirritant materials; there is no evidence in humans of hypersensitivity reactions to carbomers used topically. In humans, oral doses of 1–3 g of carbomer have been used as a bulk laxative.

LD_{50} (guinea pig, oral): 2.5 g/kg for carbomer 934[28]
LD_{50} (guinea pig, oral): 2.5 g/kg for carbomer 934P
LD_{50} (guinea pig, oral): 2.5 g/kg for carbomer 940
LD_{50} (mouse, IP): 0.04 g/kg for carbomer 934P
LD_{50} (mouse, IP): 0.04 g/kg for carbomer 940
LD_{50} (mouse, IV): 0.07 g/kg for carbomer 934P
LD_{50} (mouse, IV): 0.07 g/kg for carbomer 940
LD_{50} (mouse, oral): 4.6 g/kg for carbomer 934P
LD_{50} (mouse, oral): 4.6 g/kg for carbomer 934
LD_{50} (mouse, oral): 4.6 g/kg for carbomer 940
LD_{50} (rat, oral): 10.25 g/kg for carbomer 910
LD_{50} (rat, oral): 2.5 g/kg for carbomer 934P
LD_{50} (rat, oral): 4.1 g/kg for carbomer 934
LD_{50} (rat, oral): 2.5 g/kg for carbomer 940
LD_{50} (rat, oral): > 1g/kg for carbomer 941

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation

should be minimized to avoid the risk of explosion (lowest explosive concentration is 100 g/m^3). Carbomer dust is irritating to the eyes, mucous membranes, and respiratory tract. In contact with the eye, carbomer dust is difficult to remove with water owing to the gelatinous film that forms; saline should therefore be used for irrigation purposes. Gloves, eye protection, and a dust respirator are recommended during handling.

16 Regulatory Acceptance

Included in the FDA Inactive Ingredients Guide (oral suspensions and tablets; ophthalmic, rectal, and topical preparations). Included in nonparenteral medicines licensed in Europe.

17 Related Substances

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18 Comments

A number of different carbomer grades are commercially available that vary in their molecular weight, degree of crosslinking, polymer structure, and residual components. These differences account for the specific rheological, handling, and use characteristics of each grade. Carbomer grades that have the polymer backbone modified with long-chain alkyl acrylates are used as polymeric emulsifiers or in formulations requiring increased resistance to ions.

Polycarbophil, poly(acrylic acid) polymers crosslinked with divinyl glycol, is available for bioadhesive or medicinal applications. Carbomers designated with the letter 'P', e.g. carbomer 971P, are the only pharmaceutical grades of polymer accepted for oral or mucosal contact products. These resins are particularly useful in the production of clear gels.

19 Specific References

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21 Authors

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Polymethacrylates

1 Nonproprietary Names

BP: Methacrylic acid–ethyl acrylate copolymer (1 : 1)
Methacrylic acid–ethyl acrylate copolymer (1 : 1) dispersion 30 per cent
Methacrylic acid–methyl methacrylate coploymer (1 : 1)
Methacrylic acid–methyl methacrylate copolymer (1 : 2)

PhEur: Acidum methacrylicum et ethylis acrylas polymerisatum 1 : 1
Acidum methacrylicum et ethylis acrylas polymerisatum 1 : 1 dispersio 30 per centum
Acidum methacrylicum et methylis methacrylas polymerisatum 1 : 1
Acidum methacrylicum et methylis methacrylas polymerisatum 1 : 2

USPNF: Ammonio methacrylate copolymer
Methacrylic acid copolymer
Methacrylic acid copolymer dispersion

Note that three separate monographs applicable to polymethacrylates are contained in the USPNF 20; *see* Section 9. Several different types of material are defined in the monographs. The PhEur 2002 contains four separate monographs applicable to polymethacrylates.

2 Synonyms

Eastacryl 30D; *Eudragit*; *Kollicoat MAE 30 D*; *Kollicoat MAE 30 DP*; polymeric methacrylates.

3 Chemical Name and CAS Registry Number

See Table I.

4 Empirical Formula and Molecular Weight

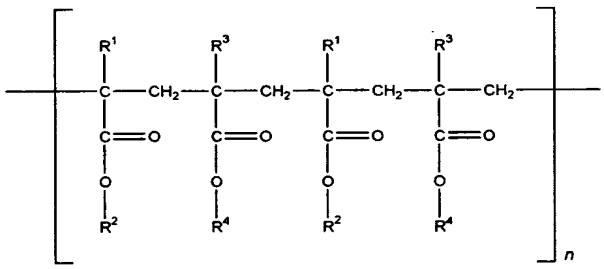
The PhEur 2002 describes methacrylic acid–ethyl acrylate copolymer (1 : 1) as a copolymer of methacrylic acid and ethyl acrylate having a mean relative molecular mass of about 250 000. The ratio of carboxylic groups to ester groups is about 1 : 1. It may contain suitable surfactants such as sodium dodecyl sulfate or polysorbate 80. An aqueous 30% w/v dispersion of this material is also defined in a separate monograph. Methacrylic acid–methyl methacrylate copolymer (1 : 1) is described in the PhEur 2002 as a copolymer of methacrylic acid and methyl methacrylate having a mean relative molecular mass of about 135 000. The ratio of carboxylic acid to ester groups is about 1 : 1. A further monograph in the PhEur 2002 describes methacrylic acid–methyl methacrylate copolymer (1 : 2), where the ratio of carboxylic acid to ester groups is about 1 : 2.

The USPNF 20 describes methacrylic acid copolymer as a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. Three types, Type A, Type B, and Type C, are defined in the monograph. They vary in their methacrylic acid content and solution viscosity. Type C may contain suitable surface-active agents. Two additional polymers, Type A (*Eudragit RL*) and Type B (*Eudragit RS*), also referred to as ammonio methacrylate copolymers, consisting of fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, are also described in the USPNF 20. A further monograph for an aqueous dispersion of Type C methacrylic acid copolymer is also defined.

See Section 9.

Typically, the molecular weight of the polymer is $\geqslant 100\,000$.

5 Structural Formula



For *Eudragit E*:
R^1, R^3 = CH_3
R^2 = $CH_2CH_2N(CH_3)_2$
R^4 = CH_3, C_4H_9

For *Eudragit L* and *Eudragit S*:
R^1, R^3 = CH_3
R^2 = H
R^4 = CH_3

For *Eudragit RL* and *Eudragit RS*:
R^1 = H, CH_3
R^2 = CH_3, C_2H_5
R^3 = CH_3
R^4 = $CH_2CH_2N(CH_3)_3^+Cl^-$

For *Eudragit NE 30 D*:
R^1, R^3 = H, CH_3
R^2, R^4 = CH_3, C_2H_5

For *Eudragit L 30 D-55* and *Eudragit L 100-55*, *Eastacryl 30D*, *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*:
R^1, R^3 = H, CH_3
R^2 = H
R^4 = CH_3, C_2H_5

6 Functional Category

Film former; tablet binder; tablet diluent.

7 Applications in Pharmaceutical Formulation or Technology

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents.[1–15] Depending on the type of polymer used, films of different solubility characteristics can be produced; *see* Table II.

Table I: Chemical name and CAS Registry Number of polymethacrylates.

Chemical name	Trade name	Company name	CAS number
Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1 : 2 : 1	*Eudragit E 100*	Röhm GmbH	[24938-16-7]
	Eudragit E 12.5	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate) 2 : 1	*Eudragit NE 30 D* (formerly *Eudragit 30 D*)	Röhm GmbH	[9010-88-2]
Poly(methacrylic acid, methyl methacrylate) 1 : 1	*Eudragit L 100*	Röhm GmbH	[25806-15-1]
	Eudragit L 12.5	Röhm GmbH	
	Eudragit L 12.5 P	Röhm GmbH	
Poly(methacrylic acid, ethyl acrylate) 1 : 1	*Eudragit L 30 D-55*	Röhm GmbH	[25212-88-8]
	Eudragit L 100-55	Röhm GmbH	
	Eastacryl 30D	Eastman Chemical	[25212-88-8]
	Kollicoat MAE 30 D	BASF Fine Chemicals	[25212-88-8]
	Kollicoat MAE 30 DP	BASF Fine Chemicals	
Poly(methacrylic acid, methyl methacrylate) 1 : 2	*Eudragit S 100*	Röhm GmbH	[25086-15-1]
	Eudragit S 12.5	Röhm GmbH	
	Eudragit S 12.5 P	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.2	*Eudragit RL 100*		[33434-24-1]
	Eudragit RL PO	Röhm GmbH	
	Eudragit RL 30 D	Röhm GmbH	
	Eudragit RL 12.5	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1	*Eudragit RS 100*		[33434-24-1]
	Eudragit RS PO	Röhm GmbH	
	Eudragit RS 30 D	Röhm GmbH	
	Eudragit RS 12.5	Röhm GmbH	

Eudragit E is used as a plain or insulating film former; it is soluble in gastric fluid below pH 5. In contrast, *Eudragit L* and *S* types are used as enteric coating agents because they are resistant to gastric fluid. Different types are available that are soluble at different pH values: e.g., *Eudragit L 100* is soluble at pH > 6; *Eudragit S 100* is soluble at pH > 7.

Eudragit RL, *RS*, and *NE 30 D* are used to form water-insoluble film coats for sustained-release products. *Eudragit RL* films are more permeable than those of *Eudragit RS*, and films of varying permeability can be obtained by mixing the two types together.

Eudragit L 30 D-55 is used as an enteric coating film former for solid-dosage forms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5.

Eudragit L 100-55 is an alternative to *Eudragit L 30 D-55*. It is commercially available as a redispersible powder.

Eastacryl 30D, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP*, are aqueous dispersions of methacrylic acid–ethyl acrylate copolymers. They are also used as enteric coatings for solid-dosage forms.

Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct-compression processes in quantities of 10–50%.

Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration.[16]

See also Section 18.

8 Description

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60 : 40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent. *See* Tables I and III.

Eudragit E is cationic polymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It is soluble in gastric fluid as well as in weakly acidic buffer solutions (up to pH ≈ 5). *Eudragit E* is available as a 12.5% ready-to-use solution in propan-2-ol–acetone (60 : 40). It is light yellow in color with the characteristic odor of the solvents. Solvent-free granules contain ≈98% dried weight content of *Eudragit E*.

Eudragit L and *S*, also referred to as methacrylic acid copolymers in the USPNF 20 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1 : 1 in *Eudragit L* and approximately 1 : 2 in *Eudragit S*. Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alkalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. They are available as a 12.5% solution in propan-2-ol without plasticizer (*Eudragit L 12.5* and *S 12.5*); and as a 12.5% ready-to-use solution in propan-2-ol with 1.25% dibutyl phthalate as plasticizer (*Eudragit L 12.5 P* and *S 12.5 P*). Solutions are colorless, with the characteristic odor of the solvent. *Eudragit L-100* and *Eudragit S-100* are white free-flowing powders with at least 95% of dry polymers.

Table II: Summary of properties and uses of commercially available polymethacrylates.

Type	Supply form	Polymer dry weight content	Recommended solvents or diluents	Solubility	Applications
Eudragit (Röhm GmbH)					
Eudragit E 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit E 100	Granules	98%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit L 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100-55	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit L 30 D-55	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit S 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit RL 12.5	Organic solution	12.5%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL 100	Granules	97%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL PO	Powder	97%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL 30 D	Aqueous dispersion	30%	Water	High permeability	Sustained release
Eudragit RS 12.5	Organic solution	12.5%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 100	Granules	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS PO	Powder	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 30 D	Aqueous dispersion	30%	Water	Low permeability	Sustained release
Eudragit NE 30 D	Aqueous dispersion	30% or 40%	Water	Swellable, permeable	Sustained release, tablet matrix
Eastacryl (Eastman Chemical Company)					
Eastacryl 30 D	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Kollicoat (BASF Fine Chemicals)					
Kollicoat 30 D	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Kollicoat 30 DP	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings

Note: Recommended plasticizers for the above polymers include dibutyl phthalate, polyethylene glycols, triethyl citrate, triacetin, and 1,2-propylene glycol. The recommended concentration of the plasticizer is approximately 10–25% plasticizer (based on the dry polymer weight). A plasticizer is not necessary with *Eudragit E 12.5*, *Eudragit E 100* and *Eudragit NE 30 D*.

Eudragit RL and *Eudragit RS*, also referred to as ammonio methacrylate copolymers in the USPNF 20 monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters, with *Eudragit RL* (Type A) having 10% of functional quaternary ammonium groups and *Eudragit RS* (Type B) having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Both polymers are water-insoluble, and films prepared from *Eudragit RL* are freely permeable to water, whereas, films prepared from *Eudragit RS* are only slightly permeable to water. They are available as 12.5% ready-to-use solutions in propan-2-ol–acetone (60 : 40). Solutions are colorless or slightly yellow in color, and may be clear or slightly turbid; they have an odor characteristic of the solvents. Solvent-free granules (*Eudragit RL 100* and *Eudragit RS 100*) contain ⩾97% of the dried weight content of the polymer.

Eudragit RL PO and *Eudragit RS PO* are fine, white powders with a slight aminelike odor. They are characteristically the same polymers as *Eudragit RL* and *RS*. They contain ⩾97% of dry polymer.

Eudragit RL 30 D and *Eudragit RS 30 D* are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. The dispersions contain 30% polymer. The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers. Films prepared from *Eudragit RL 30 D* are readily permeable to water and to dissolved active substances, whereas films prepared from *Eudragit RS 30 D* are less permeable to water. Film coatings prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties.

Table III: Solubility of commercially available polymethacrylates in various solvents.

Type	Solvent						
	Acetone and alcohols[a]	Dichloromethane	Ethyl acetate	1 N HCl	1 N NaOH	Petroleum ether	Water
Eudragit (Röhm GmbH)							
Eudragit E 12.5	M	M	M	M	–	M	–
Eudragit E 100	S	S	S	–	–	I	I
Eudragit L 12.5 P	M	M	M	–	M	P	P
Eudragit L 12.5	M	M	M	–	M	P	P
Eudragit L 100-55	S	I	I	–	S	I	I
Eudragit L 100	S	I	I	–	S	I	I
Eudragit L 30 D-55[b]	M[c]	–	–	M[d]	–	M	
Eudragit S 12.5 P	M	M	M	–	M	P	P
Eudragit S 12.5	M	M	M	–	M	P	P
Eudragit S 100	S	I	I	–	S	I	I
Eudragit RL 12.5	M	M	M	–	–	P	M
Eudragit RL 100	S	S	S	–	–	I	I
Eudragit RL PO	S	S	S	–	I	I	I
Eudragit RL 30 D	M[e]	M	M	–	I	I	M
Eudragit RS 12.5	M	M	M	–	–	P	M
Eudragit RS 100	S	S	S	–	–	I	I
Eudragit RS PO	S	S	S	–	I	I	I
Eudragit RS 30 D	M[e]	M	M	–	I	I	M
Eastacryl (Eastman Chemical Company)							
Eastacryl 30D[b]	M[c]	–	–	–	M[d]	–	M
Kollicoat (BASF Fine Chemicals)							
Kollicoat MAE 30 D[b]	M[c]	–	–	–	M[d]	–	M
Kollicoat MAE 30 DP[b]	M[c]	–	–	–	M[d]	–	M

S = soluble; M = miscible; I = insoluble or immiscible; P = precipitates.

[a] Alcohols including ethanol, methanol, and propan-2-ol.

[b] Supplied as a milky-white aqueous dispersion.

[c] A 1 : 5 mixture forms a clear, viscous, solution.

[d] A 1 : 2 mixture forms a clear or slightly opalescent, viscous liquid.

1 part of *Eudragit RL 30 D* or of *Eudragit RS 30 D* dissolves completely in 5 parts acetone, ethanol, or propan-2-ol to form a clear or slightly turbid solution. However, when mixed in a ratio of 1 : 5 with methanol, *Eudragit RL 30 D* dissolves completely, whereas *Eudragit RS 30 D* dissolves only partially.

Eudragit NE 30 D is an aqueous dispersion of a neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. Films prepared from the lacquer swell in water, to which they become permeable. Thus, films produced are insoluble in water, but give pH-independent drug release.

Eudragit L 30 D-55, is an aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer corresponds to USPNF 20 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1 : 1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media but soluble in the small intestine.

Eastacryl 30D, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP* are also aqueous dispersions of the anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer also corresponds to USPNF 20 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1 : 1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media, but soluble in the small intestine.

Eudragit L 100-55 (prepared by spray-drying *Eudragit L 30 D-55*) is a white, free-flowing powder that is redispersible in water to form a latex that has properties similar to those of *Eudragit L 30 D-55*.

9 Pharmacopeial Specifications

Specifications for polymethacrylates from the PhEur 2002 are shown in Table IV and those from the USPNF 20 in Table V.

10 Typical Properties

Acid value:
300–330 for *Eudragit L 12.5*, *L 12.5 P*, *L 100*, *L 30 D-55*, *L 100-55*; *Eastacryl 30D*; *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP*
180–200 for *Eudragit S 12.5*, *S 12.5 P*, and *S 100*

Alkali value:
162–198 for *Eudragit E 12.5* and *E 100*
23.9–32.3 for *Eudragit RL 12.5*, *RL 100*, and *RL PO*
27.5–31.7 for *Eudragit RL 30 D*
12.1–18.3 for *Eudragit RS 12.5*, *RS 100*, and *RS PO*
16.5–22.3 for *Eudragit RS 30 D*

Density (bulk): 0.390 g/cm^3
Density (tapped): 0.424 g/cm^3

Table IV: Specifications from PhEur 2002.

Test	PhEur 2002			
	Methacrylic acid–ethyl acrylate copolymer (1 : 1)	Methacrylic acid–ethyl acrylate copolymer (1 : 1) dispersion 30%	Methacrylic acid–methyl methacrylate copolymer (1 : 1)	Methacrylic acid–methyl methacrylate copolymer (1 : 2)
Identification	+	+	+	+
Characters	+	+	+	+
Appearance of a film	+	+	+	+
Apparent viscosity	+	⩽15 mPa s	50–200 mPa s	—
Particulate matter	—	⩽1.0%	—	—
Ethyl acrylate and methacrylic acid	⩽0.1%	⩽0.1%	—	—
Methyl methacrylate and methacrylic acid	—	—	⩽0.1%	⩽0.1%
Residue on evaporation	—	28.5–31.5%	—	—
Loss on drying	⩽5.0%	—	⩽5.0%	⩽5.0%
Sulfated ash	⩽0.4%	⩽0.2%	⩽0.1%	⩽0.1%
Microbial contamination	—	+	—	—
Assay (methacrylic acid units)	46.0–50.6%	46.0–50.6%	46.0–50.6%	27.6–30.7%

Density (true):
0.811–0.821 g/cm^3 for *Eudragit E*
0.83–0.85 g/cm^3 for *Eudragit L, S 12.5* and *12.5 P*
0.831–0.852 g/cm^3 for *Eudragit L, S 100*
1.062–1.072 g/cm^3 for *Eudragit L 30 D-55*
0.821–0.841 g/cm^3 for *Eudragit L 100-55*
0.816–0.836 g/cm^3 for *Eudragit RL* and *RS 12.5*
0.816–0.836 g/cm^3 for *Eudragit RL* and *RS PO*
1.047–1.057 g/cm^3 for *Eudragit RL* and *RS 30 D*
1.037–1.047 g/cm^3 for *Eudragit NE 30D*
1.062–1.072 g/cm^3 for *Eastacryl 30D*
1.062–1.072 g/cm^3 for *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*

Refractive index:
n_D^{20} = 1.38–1.385 for *Eudragit E*
n_D^{20} = 1.39–1.395 for *Eudragit L* and *S*
n_D^{20} = 1.387–1.392 for *Eudragit L 100-55*
n_D^{20} = 1.38–1.385 for *Eudragit RL* and *RS*

Solubility: *see* Table II.

Viscosity (dynamic):
3–12 mPa s for *Eudragit E*
⩽50 mPa s for *Eudragit NE 30D*
50–200 mPa s for *Eudragit L* and *S*
⩽15 mPa s for *Eudragit L 30 D-55*
100–200 mPa s for *Eudragit L 100-55*
⩽15 mPa s for *Eudragit RL* and *RS*
⩽200 mPa s for *Eudragit RL* and *RS 30D*
⩽15 mPa s for *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*
145 mPa s for *Eastacryl 30D*

11 Stability and Storage Conditions

Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can readily be broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

Dispersions are sensitive to extreme temperatures and phase separation occurs below 0°C. Dispersions should therefore be stored at temperatures between 5 and 25°C and are stable for at least 18 months after shipping from the manufacturer's warehouse if stored in a tightly closed container at the above conditions.

12 Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; *see* Table II. For example, dispersions of *Eudragit L 30 D*, *RL 30 D*, *L 100-55*, and *RS 30 D* are incompatible with magnesium stearate. *Eastacryl 30D*, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP* are also incompatible with magnesium stearate.

Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

13 Method of Manufacture

Prepared by the polymerization of acrylic and methacrylic acids or their esters, e.g., butyl ester or dimethylaminoethyl ester.

14 Safety

Polymethacrylate copolymers are widely used as film-coating materials in oral pharmaceutical formulations. They are also used in topical formulations and are generally regarded as nontoxic and nonirritant materials.

A daily intake of 2 mg/kg body-weight of *Eudragit* (equivalent to approximately 150 mg for an average adult) may be regarded as essentially safe in humans.

See also Section 15.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Additional measures should be taken when handling organic solutions of polymethacrylates. Eye protection, gloves, and a dust mask or respirator are recommended. Polymethacrylates should be handled in well-ventilated environment and measures should be taken to prevent dust formation.

Table V: Specifications from USPNF 20.

Test	USPNF 20	USPNF 20 (Suppl 1)
	Ammonio methacrylate copolymer[a]	Methacrylic acid copolymer
Identification	+	+
Viscosity		
Type A	≤15 mPa s	50–200 mPa s
Type B	≤15 mPa s	50–200 mPa s
Type C	–	100–200 mPa s
Loss on drying		
Type A	≤3.0%	≤5.0%
Type B	≤3.0%	≤5.0%
Type C	–	≤5.0%
Residue on ignition		
Type A	≤0.1%	≤0.1%
Type B	≤0.1%	≤0.1%
Type C	–	≤0.4%
Arsenic	–	≤2 ppm
Heavy metals	≤0.002%	≤0.002%
Organic volatile impurities	–	+
Limit of monomers	–	≤0.05%
Methyl methacrylate	≤0.005%	–
Ethyl acrylate	≤0.025%	–
Assay of methacrylic acid units (dried basis)		
Type A	8.85–11.96%	46.0–50.6%
Type B	4.48–6.77%	27.6–30.7%
Type C	–	46.0–50.6%

[a] Corresponds to *Eudragit RL* and *RS*.

Acute and chronic adverse effects have been observed in workers handling the related substances methyl methacrylate and poly(methyl methacrylate) (PMMA).[17,18] In the UK, the occupational exposure limit for methyl methacrylate has been set at 208 mg/m^3 (50 ppm) long-term (8-hour TWA), and 416 mg/m^3 (100 ppm) short-term.[19]

See also Section 17.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Methyl methacrylate; poly(methyl methacrylate).

Methyl methacrylate

Empirical formula: $C_5H_8O_2$
Molecular weight: 100.13
CAS number: [80-62-6]
Synonyms: methacrylic acid, methyl ester; methyl 2-methacrylate; methyl 2-methylpropenoate; MME.
Safety:

LD_{50} (dog, SC): 4.5 g/kg
LD_{50} (mouse, IP): 1 g/kg
LD_{50} (mouse, oral): 5.2 g/kg
LD_{50} (mouse, SC): 6.3 g/kg
LD_{50} (rat, IP): 1.33 g/kg
LD_{50} (rat, SC): 7.5 g/kg

Comments: methyl methacrylate forms the basis of acrylic bone cements used in orthopedic surgery.

Poly(methyl methacrylate)

Empirical formula: $(C_5H_8O_2)_n$
Synonyms: methyl methacrylate polymer; PMMA.
Comments: poly(methyl methacrylate) has been used as a material for intraocular lenses, for denture bases, and as a cement for dental prostheses.

18 Comments

A number of different polymethacrylates are commercially available that have different applications and properties; *see* Table II.

For spray coating, polymer solutions and dispersions should be diluted with suitable solvents. Some products need the addition of a plasticizer such as dibutyl sebacate, dibutyl phthalate, glyceryl triacetate, or polyethylene glycol. Different types of plasticizer may be mixed to optimize the polymer properties for special requirements.

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21 Authors

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22 Date of Revision

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Enteric coatings with EUDRAGIT® L/S from aqueous dispersions

Application Technology Sheet

Active crystals coated with EUDRAGIT L 30 D-55

Operating method

This leaflet describes a spraying process for the manufacture of colourless enteric sealing coats with EUDRAGIT L 30 D-55 on active crystals (acetylsalicylic acid).

Ideal structures for such coating processes are evenly shaped, compact crystals or granules. Crystal needles or porous particle agglomerates are less suitable, since they break easily or soak up the dispersion.

The coating suspension is sprayed onto the fluidized particles, which are prewarmed to about 30 °C, by means of an air spray gun (top-spray method). Spray rate, inlet air quantitiy and inlet air temperature are adjusted in such a way that spraying can be performed continuously. During the process, the crystals should be maintained at a temperature of 25 to 30 °C and be able to flow freely.

Agglomeration can be avoided by adding suitable glidants (talc, glycerol monostearate, kaolin, Syloid®) to the EUDRAGIT L 30 D-55 spray suspension.

If agglomeration does occur, spraying must be interrupted until the active particles are dry and once more able to float freely. Subsequently, processing may be continued at a reduced spray rate.

To improve the flow of small particles, lubricants such as Aerosil® 200, talc or magnesium stearate (0.2 to 0.5 %) can be added.

The following polymers, dissolved in organic solvents, are recommended for subcoating of extremely water-sensitive active ingredients:
EUDRAGIT E 12,5; EUDRAGIT E 100
EUDRAGIT RL/RS 12,5
EUDRAGIT RL/RS 100
EUDRAGIT L/S 12,5
EUDRAGIT L/S 100
EUDRAGIT L 100-55

Given adequate heating capacity and a sufficient amount of drying air, rapid and effective drying of the coated crystals is ensured.

Similarly to colloidal systems, aqueous dispersions are adversely affected by various factors. Coagulation may occur in the presence of electrolytes, organic solvents or finely dispersed pigments, due to changes in pH, foam formation, heat or frost, or high shear in high-speed mixers and mills.

Finely dispersed pigments in polymer dispersions may cause speckling. Added emulsifiers (polysorbate, polyethylene glycol, polyvinyl pyrrolidone, Na carboxymethylcellulose, etc.) have a stabilizing effect. When speckling leads to coagulation, these dispersions cannot be redispersed and must be discarded. Therefore, you are advised to follow our instructions as far as work steps and excipient ratios are concerned.

Dispersions of EUDRAGIT L 30 D-55 are incompatible with magnesium stearate (thickening or coagulation), but magnesium stearate contained in tablets affects neither the spray suspension nor the film properties.

Special precautions

- Make sure that the workplaces are always sufficiently ventilated.
- Bear in mind the fire hazard and toxicity of organic solvents.
- When handling powders, take measures to prevent static discharges. Observe the machine manufacturer's instructions for protection against explosion or the pertinent official regulations.